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Preliminary Risk Characterization for Acetyl Tributyl Citrate Used as a Plasticizer in Polyvinyl Chloride Children's Toys

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Executive Summary

The use of phthalate esters in children's polyvinyl chloride (PVC) toys has come under intense scrutiny over the last several years in Europe, Canada and the U.S., because of concern for potential long-term health effects to children exposed to phthalates via normal mouthing of these types of PVC products. Because of its suitable technical properties as a PVC plasticizer and its low toxicity, acetyl tributyl citrate (ATBC) has been suggested as an appropriate replacement for DINP in this application.

The risk characterization procedure used in this report, i.e. comparison of an acceptable daily intake (ADI) to an estimated daily intake (EDI) for humans, is the procedure most commonly applied by regulatory authorities and the scientific community at large. In the first step of the risk characterization procedure, hazard characterization, the no-observed-adverse-effect-level (NOAEL) from a two-generation reproductive toxicity study conducted with ATBC in rats was established as 100 mg/kg/day. The ADI was derived by dividing the NOAEL by an overall uncertainty factor of 100, resulting in an ADI of 1 mg/kg/day or 1000 µg/kg/day.

Since experimental migration data simulating children's normal mouthing of ATBC plasticized PVC toys were not available for the estimation of children's potential exposure to ATBC, the relevant DINP database was used to provide surrogate data for the exposure assessment of ATBC. In an experiment in which ATBC or DINP migration from PVC test samples by saliva simulant extraction was investigated under identical laboratory testing conditions, it was observed that significantly less ATBC was extracted over the same time period as compared to the amount of DINP that was extracted. Therefore, based on this experimental data comparing ATBC and DINP extraction by saliva simulant, it would be expected that, in real-life situations of children mouthing ATBC or DINP plasticized PVC toys, ATBC would migrate to a lesser degree than DINP and, subsequently, less ATBC would be available for ingestion.

During December 1998 the U.S. Consumer Product Safety Commission (U.S. CPSC 1998) released its investigation entitled "The Risk of Chronic Toxicity Associated with Exposure to Diisononyl Phthalate (DINP) in Children's Products". As compared to the recent reports of the Dutch Consensus Group and Health Canada, the CPSC report provided much more detail with regard to methods and results and appeared in many respects to be a scientifically more complete piece of work than the other two studies. The CPSC was selected as the most appropriate study for the estimation of children's exposure to DINP through normal mouthing of plasticized PVC toys and, subsequently, the information in that report was used as the model to estimate the potential exposure for children mouthing ATBC plasticized PVC toys.

Comparison of the EDIs derived for ATBC from the relevant DINP database, even assuming the most extreme exposure scenarios presented in the U.S. CPSC report, and the ADI from a two-generation reproductive toxicity study conducted with ATBC, indicated a low Relative Risk of long-term health effects for children using ATBC plasticized PVC toys.

Introduction

Phthalate esters have been used for decades as plasticizers for polyvinyl chloride (PVC) articles and are considered to be the most ubiquitous of all industrial chemicals. They are used in a variety of PVC applications such as automobile components, electrical cables, construction materials, food packaging, medical articles and children's toys and products. The long-term toxicity of phthalate esters has been investigated extensively beginning about 20 years ago, particularly with regard to chronic and carcinogenic effects, and more recently with regard to reproductive, developmental and endocrine effects. Also, beginning in the mid-1980s, di(2-ethylhexyl) phthalate (DEHP), and more recently, diisononyl phthalate (DINP), have been evaluated for their potential to migrate from PVC toys under experimental conditions simulating children's normal mouthing activity.

The use of phthalate esters in children's PVC toys has come under intense scrutiny over the last several years by public interest groups and regulatory authorities in Europe, Canada and the U.S., because of concern for potential long-term health effects to children exposed to these chemicals via mouthing of these types of PVC products. Consequently, public interest groups, as well as some regulatory authorities, have suggested that phthalate esters should be replaced in children's PVC toys by alternative plasticizers. Because of its suitable technical properties as a PVC plasticizer and its low toxicity, acetyl tributyl citrate (ATBC) has been suggested as an appropriate replacement for DINP, which is currently the dominant plasticizer used in the children's PVC toys application.

Overview of the Risk Characterization Procedure

The risk characterization procedure used in this report, i.e. comparison of an acceptable daily intake (ADI) to an estimated daily intake (EDI) for humans, is the procedure most commonly applied by regulatory authorities and the scientific community at large. ADIs and EDIs are derived from experimental data. The keys elements of a risk characterization are as follows:

- Hazard characterization is performed. Hazard characterization is a description of the most biologically relevant health effects associated with exposure to a chemical in laboratory animal toxicology studies, together with information on doses likely to elicit these effects. Hazard characterization requires gathering and evaluating information needed for hazard identification and dose-response assessment. Hazard identification means identifying the potentially dangerous properties of a chemical. Dose-response assessment is the characterization of the relationship between the dose (exposure) of a chemical and the anticipated incidence of an adverse health effect in an exposed population.
- From hazard characterization, a no-observed-adverse-effect-level (NOAEL) is determined for the "critical health effect". A NOAEL is the dose of a chemical at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed laboratory animal population and its appropriate control (Lewis *et al.* 1990). A no-observed-effect-level NOEL is subtly different from a NOAEL in that a NOEL is determined by any effect in the exposed laboratory animal population as compared to its appropriate control, even if that effect is not considered to be adverse. The

"critical health effect" refers to the specific adverse health effect on which the risk characterization is based. That critical health effect may not be the most sensitive of all effects, but it is the most sensitive adverse effect (i.e. of toxicological significance). The U.S. EPA (cited in: Dourson and Stara 1983) defined "adverse effect" as "functional impairment or pathological lesions which may affect the performance of the organism as a whole or which reduce an organism's ability to respond to an additional challenge."

- The NOAEL from a toxicology study is then adjusted by uncertainty factors to derive an ADI for humans. The ADI for humans is normally derived by applying uncertainty factors to the highest NOAEL from appropriate toxicology studies. The uncertainty factor should take into consideration the following (Lewis *et al.* 1990):
  - Known differences between laboratory animals and humans, and the uncertainties of extrapolating animal data to humans;
  - Variations in the sensitivity of the exposed human population;
  - Strength of evidence that a chemical presents a real hazard to human health;
  - Type and severity of the putative adverse health effect;
  - Potency of the toxic agent; and
  - Quality of the toxicology database, including known differences between experimental conditions and real life exposures.
- Exposure assessment is performed. The objective of exposure assessment is to determine an EDI, which is the predicted average amount of a chemical that an individual in a human population will receive as a result of an activity that places them in contact with a chemical. The estimate is based on identifying and quantifying the potential exposures in terms of magnitude, frequency, duration and route of exposure for a chemical to humans.
- Risk characterization is performed. Risk characterization is a description of the nature and magnitude of health risk. The description combines results of hazard characterization and exposure assessment, and describes the uncertainty associated with each step. Mathematically this comparison can be expressed as:

$$\text{Relative Risk} = \frac{\text{EDI}}{\text{ADI}} \qquad (1)$$

- In cases where the Relative Risk ratio is much greater than "1", risk is high because the EDI is higher than the ADI.
- In cases where the Relative Risk ratio is much less than "1", risk is low because the EDI is lower than the ADI.
- In cases where the Relative Risk ratio is about "1", risk is indeterminate and improved toxicology and/or exposure data are probably needed.
- Risk characterization is normally an iterative process whereby the application of new toxicology and/or exposure data can be used to improve the quality and accuracy of the risk characterization.

Hazard Characterization for ATBC

The short-term and long-term toxicological effects of ATBC have been assessed and summarized previously (Nikiforov 1999) and will not be discussed in detail in the current report, except to identify the critical health effect and its NOAEL.

ATBC has been evaluated in rat and dog two-year toxicity studies, although these studies were conducted before the introduction of Good Laboratory Practice (GLP) Standards. However, the results of these chronic toxicity studies are concordant with the results of a 90-day oral subchronic toxicity study conducted in rats in accordance with GLPs and, therefore, do have utility for hazard characterization purposes. The NOAEL for the subchronic and chronic toxicity studies conducted in rats was 1000 mg/kg/day in both cases. The NOAEL in the dog chronic toxicity study was 140 mg/kg/day, which was the highest dose tested in that study. Therefore, it can be concluded that ATBC possesses very low systemic toxicity potential in adult laboratory animals via the oral route of administration, since no treatment-related toxic effects were seen at the highest doses tested in one modern subchronic and two chronic toxicity studies.

Although chronic and subchronic toxicity studies are important for the identification of toxic effects to target organs, in this particular risk characterization, for which the concern for health effects is focussed on young children, a more appropriate study design should involve a lifecycle assessment for adverse health effects potential. The most appropriate study design for this type of evaluation is a two-generation reproductive toxicity study. This study design provides for exposure of the experimental animals of the first generation *in utero*, during lactation, puberty and adulthood. The reproductive performance of the first generation adults is then evaluated by their ability to produce normal healthy offspring.

A two-generation reproductive toxicity study was conducted with ATBC in rats recently, in accordance with GLPs. Dietary treatment of rats with ATBC at doses of up to 1000 mg/kg/day did not cause any adverse histopathological or reproductive effects, and no lesions were seen in the second generation offspring. Treatment was associated with some minor changes, including the following statistically significantly effects as compared to control animals: decreased water intake in the parental and first generation females during pregnancy and in parental and first generation males during adolescence and as young adults in the 1000 mg/kg/day dose group; decreased body weights during the lactation period for the first and second generation offspring (males and females were not identified until Day 21 postpartum) in the 1000 mg/kg/day dose group; and decreased body weights in first generation males during Days 0 to 114 after weaning in both the 300 and 1000 mg/kg/day dose groups.

The decreased first generation male body weights was determined to be the critical health effect, and the NOAEL was established at 100 mg/kg/day under the experimental conditions of this study.

Evaluation of Extraction Studies Available for ATBC

Since the objective is to understand the potential for exposure of young children to ATBC migrating from PVC toys through normal mouthing activities (sucking and chewing), data from experimental migration studies using saliva simulant or conducted in human volunteers are preferred.

Virtually all the published migration studies on ATBC deal with its migration from plastic film into food or food simulants (see Appendix A). These studies are not useful for the estimation of ATBC migration from PVC toys through children's normal mouthing activities. However, pertinent information regarding ATBC migration and/or exposure was found in other sources.

ATBC is reported to be insoluble in water (BIBRA 1991; Bisesi 1994). ATBC migration into tap water has been tested (Morflex 1998). Medical grade PVC plastic stock was blended and two-roll milled for 5 to 10 minutes at 325 to 340°F. The milled stock was compression-molded for 3 minutes at 325 to 340°F and 32,000 psi to form 40 millimeter (mil) sheets, then conditioned for 48 hours at 75°F for evaluation. The test samples contained 50.00 parts by weight of ATBC. Two inch diameter specimens of the ATBC plasticized PVC were suspended in containers of tap water at 140°F for 24 hours. Under the conditions of the experiment, 1.1% of the ATBC was extracted into water, and consequently its migration into an aqueous substance such as human saliva would be expected to be low.

Recently, ATBC migration into human saliva simulant has been tested (Morflex 1999). The test samples contained 40 or 65 parts per hundred resin (phr) of ATBC or DINP with formulations produced as follows:

Table 1: Formulations of Test Samples for Morflex Saliva Extraction Study (phr)

Ingredient	ATBC (40)	ATBC (65)	DINP (40)	DINP (65)
Borden PVC	40	40	40	40
Geon PVC	60	60	60	60
ATBC	40	65	0	0
DINP	0	0	40	65
Epoxy Soya	6	6	6	6
TXIB	7.5	7.5	7.5	7.5
Stabilizer	3	3	3	3

Individual batches were preweighed in 30 pound lots and mixed with an air power mixer for approximately 15 minutes to prepare plastisol. Plastisol was fed to a 45 mm twin screw extruder at 45 rpm with maximum melt temperature at 340°F. Four strands were extruded and pelletized. Pellets were fed to an injection molder with cycle time of approximately 55 seconds. Molded specimens were circles approximately two inches in diameter and 40 mils thick. Specimens were held at approximately 77°F for at least 24 hours before testing.

Test specimens were rinsed with isopropanol and air or nitrogen dried to clean the surfaces. Specimens were then weighed to ± 0.0001 gram (g). Specimens of the ATBC or DINP plasticized PVC were each suspended in individual containers of saliva simulant at 140°F for 24 hours. All surfaces of the test specimens were in contact with the saliva simulant extraction medium. The saliva simulant consisted of the following substances added to 1-liter of distilled water (Morflex 1999):

Formula	g/liter
$MgCl_2$	0.078
$CaCl_2$	0.110
K_2HPO_4	0.569
K_2CO_3	0.530
NaCl	0.330
KCl	0.745
Mucin	1.600

Following the extraction period, the specimens were removed from the saliva simulant and cleaned with wiping and isopropanol washes to remove all traces of the extraction medium. Subsequently, specimens were oven dried at 104°F for 30 minutes and placed in a desiccator to cool. Specimens were reweighed in order to have a gross measurement of total mass lost during the 24-hour extraction test. Loss of ATBC or DINP from the test samples under the experimental conditions described above was determined in triplicate by an HPLC system fitted with a variable wavelength UV detector. Approximately 20 mg samples were cut from the test specimens, weighed, placed in a 10.0 ml volumetric flask and dissolved in 3.0 ml of HPLC grade tetrahydrofuran using approximately 60 minutes of sonication and occasional shaking. When the plastic was completely dissolved, eluent was added to volume. Eluent for ATBC samples was 75% acetonitrile/25% water and for DINP samples it was 95% acetonitrile/5% water. The volumetric flask was shaken vigorously to induce precipitation of the polymer. After allowing approximately 5 minutes for precipitation, a sample was withdrawn using a 1 ml glass syringe and was injected through a 0.45 µm filter disk into the HPLC. Peak area produced by each of the samples was compared to previously developed standard curves in order to quantify the percentage of plasticizer remaining in samples after the extraction experiments. The data are summarized in the following table (Morflex 1999).

Table 2: % Plasticizer Loss by Saliva Simulant Extraction

Plasticizer Content of PVC Samples (phr)	ATBC (% loss)	DINP (% loss)	Extraction Ratio ATBC:DINP
40	0.8	3.4	0.24
65	2.0	6.1	0.33

The data from this experiment indicate that, under the identical testing conditions described above, ATBC migrates from plasticized PVC to saliva simulant, on average, at less than

one-third (0.29) the rate of DINP. However, it should be recognized that these are initial data and this experiment has not yet been replicated.

Exposure Assessments for ATBC and DINP

The migration of DINP from plasticized PVC samples or pieces of vinyl toys to saliva simulant or human saliva was investigated in 1997-1998 by the Health Canada Product Safety Laboratory (Health Canada 1998), the Netherlands National Institute of Public Health and the Environment (RIVM 1998) for the Dutch Consensus Group and the U.S. Consumer Product Safety Commission (U.S. CPSC 1998). Since migration data for the estimation of children's exposure to ATBC by normal mouthing of ATBC plasticized PVC toys are not available, the extensive database of DINP can be used to provide surrogate data for the exposure assessment of ATBC. Based on the data presented above for % ATBC or DINP loss by saliva simulant extraction (Table 2), it can be observed that ATBC is not extracted at any greater rate than DINP under identical experimental conditions. In fact, the available data indicate that ATBC extraction by saliva simulant is about one-third of that seen with DINP. There is no reason to expect that, in real life scenarios of children mouthing ATBC or DINP plasticized PVC toys, ATBC would migrate at a rate as great as DINP. The information available suggests that, under conditions of identical plasticizer content and assuming the same behavior patterns of toy mouthing, children using ATBC plasticized PVC toys would be exposed to approximately one-third the amount of ATBC as compared to the amount of DINP to which children would be exposed using DINP plasticized PVC toys.

In December 1998, the CPSC (U.S. CPSC 1998) released its investigation entitled "The Risk of Chronic Toxicity Associated with Exposure to Diisononyl Phthalate (DINP) in Children's Products". As compared to the reports of the RIVM and Health Canada, the CPSC report provides much more detail with regard to methods and results and appears, in many respects, to be a scientifically more complete piece of work than the other two studies. CPSC conducted two studies to measure DINP migration from plasticized PVC children's toys:

1. Migration into artificial saliva using an impaction method; and
2. A human volunteers study to determine *in vivo* release rates of DINP from PVC samples into saliva during chewing.

The CPSC measured migration of DINP from children's toys using a laboratory impaction method, previously used to evaluate DEHP during the 1980s. Toys to be tested were placed in a stainless steel beaker and immersed in 50 ml of a saliva simulant at 98.6°F. A precisely controlled pneumatic piston impacted the test article to approximate the effects of children's biting or chewing. Data resulting from trials using this methodology showed DINP migration rates ranging from 1 to 48 µg/hr for a surface area of 11 cm^2. This is the estimate CPSC used as the average surface area that can fit into an infant's mouth. CPSC investigators noted that, in these experiments, DINP migration rates into the saliva simulant did not correlate with DINP content of the tested toys, manufacturing process or the wall thickness of the test articles.

The CPSC also conducted studies with 10 adult human volunteers to compare the migration rate measured *in vivo* with the migration rates measured by the impaction method. In order to have a valid comparison, disks cut from five identical plasticized PVC toys were used in both *in vivo* and impaction method studies. Subjects were instructed to move the disks in their mouths, draw upon, apply pressure with the tongue, or lightly chew the disks during four 15 minute intervals. All saliva was collected for analysis of DINP content. The *in vivo* migration rate established in 10 adult human volunteers (241.3 µg/10.3 cm^2/hr) was, on average, 39.5 times greater than the rate measured in the impaction study.

The CPSC used the children's mouthing behavior study sponsored by the Dutch Consensus Group (Groot 1998) to develop its estimates for daily mouthing duration.

The CPSC calculated the estimated daily oral exposure (equivalent to the EDI) for children mouthing plasticized PVC toys using the following equation:

$$DE\ (\text{or EDI}) = \frac{M \times R \times D}{60 \times BW} \qquad (2)$$

Where:

DE = Daily oral exposure (or EDI), µg/kg body weight/day.
M = Migration rate for an 11 cm^2 area by the impaction method, µg/hr.
R = Ratio of the migration rate with human subjects to that by impaction.
D = Duration of mouthing, min/day.
60 = Conversion from minutes to hours, min/hr.
BW = Body weight, kg.

Data for migration rates by the impaction method, the ratio between the migration rate with human subjects to that by impaction, and the duration of mouthing were fitted to lognormal distributions. The geometric means and variances of these distributions were used to estimate the geometric mean and 95th percentile values of the daily exposure, as well as 95% confidence limits for the geometric mean and 95th percentile values. Average body weights and minutes per day mouthing of toys for the 3 to 12 month old and 13 to 26 month old age groups are summarized in Table 3 below and the parameters related to the estimated daily intake of DINP in PVC toys are summarized in Table 4.

Table 3: Average Body Weights and Minutes/Day Mouthing Toys[a]

Age range (months)	Average body weight (kg)	Minutes per day mouthing toys[b]	
		Geometric mean	Standard deviation
3 - 12	7.3	12.0	2.55
13 - 26	10.7	2.1	1.75

[a] From U. S. CPSC 1998.
[b] Estimated from data in the Dutch Consensus Group study (Groot *et al.* 1998).

Table 4: EDI for DINP in PVC Toys[a]

Age range (months)	Exposure, µg/kg/day[b]	
	Average[c]	95th percentile[d]
3 - 12	5.7 (2.5 - 12.9)	94.3 (50.1 - 225.6)
13 - 26	0.7 (0.3 - 1.6)	7.6 (4.6 - 16.8)

[a] From U. S. CPSC 1998.
[b] The estimated daily intake calculated with equation (2).
[c] The numbers in parentheses are the 95% confidence intervals (Greene 1998).
[d] The 95th percentile value reflects the variance in the impaction method migration rate, the ratio of the migration rate in human volunteers to that by impaction, and the duration of mouthing activity. The numbers in parentheses are the 95% confidence intervals (Greene 1998).

Risk Characterization for ATBC

As discussed in the "Hazard Characterization for ATBC" section of this document, a two-generation reproductive toxicity study conducted with ATBC in accordance with GLPs was selected as the most appropriate available study to establish the critical health effect to be used for risk characterization. Decreased body weights in first generation males during Days 0 to 114 after weaning in both the 300 and 1000 mg/kg/day dose groups, as well as a few other minor effects seen only at 1000 mg/kg/day, were observed in this study. The decreased first generation male body weight effect was determined to be the critical health effect, and the NOAEL was established as 100 mg/kg/day under the experimental conditions of this study. The ADI for health effects seen in the two-generation reproductive toxicity study is derived by dividing the NOAEL in animals by an overall uncertainty factor of 100. The uncertainty factor is the product of two factors: 10 for interspecies variation between laboratory animals and humans and 10 for interindividual variation between humans (U. S. CPSC 1992). Therefore, in this case, the ADI is 1 mg/kg/day or 1000 µg/kg/day.

Since migration data for the estimation of children's exposure to ATBC by normal mouthing of ATBC plasticized PVC toys are not available, the extensive database of DINP can be used to provide surrogate data for the exposure assessment of ATBC. Based on the data presented in Table 2 for % ATBC or DINP loss by saliva simulant extraction, it can be observed that ATBC is not extracted at any greater a rate than DINP under identical experimental conditions; in fact, the available data indicate that ATBC extraction by saliva simulant is about one-third of that seen with DINP. Therefore, there is no reason to expect that, in real-life scenarios of children mouthing ATBC or DINP plasticized PVC toys, ATBC would migrate at a rate as great as DINP. The information available suggests that, under conditions of identical plasticizer content and assuming the same behavior patterns of toy mouthing, children using ATBC plasticized PVC toys would be exposed to approximately one-third the amount of ATBC as compared to the amount of DINP exposure for children using DINP plasticized PVC toys.

Table 5 presents Relative Risk ratios for exposure scenarios previously presented in this document. In Table 5, the exposure information for DINP presented in Table 4 is used as surrogate data for ATBC EDIs. Using Equation (1) the Relative Risk ratios are calculated from the ATBC EDIs (derived from DINP data) and the ATBC ADI. Under even the most extreme

exposure scenarios considered in the U.S. CPSC report, the EDI:ADI ratio is well below "1"; therefore, risk is low because the estimated daily intake is much lower than the acceptable daily intake. In addition, considering exposure scenarios where ATBC is assumed to migrate at a rate one-third less than DINP, the calculated EDI:ADI ratios would be one-third of the values shown in the Relative Risk column of Table 5.

Table 5: Relative Risk Ratios Assuming ATBC Migrates at the Same Rate as DINP During Children's Normal Mouthing of Plasticized PVC Toys

Age range (months)	ATBC EDI (µg/kg/day)	ATBC ADI (µg/kg/day)	Relative Risk EDI:ADI
3 - 12	5.7[a]	1000	0.0057
	94.3[b]	1000	0.0943
13 - 26	0.7[a]	1000	0.0007
	7.6[b]	1000	0.0076

[a] Average or most likely EDI from Table 4.
[b] The 95th percentile value of the EDI from Table 4.

Conclusion

The ADI for ATBC was determined using the available toxicology database for ATBC. Studies that simulate ATBC migration from plasticized PVC toys during children's normal mouthing of these objects were not available for ATBC. Therefore, EDIs for children's normal mouthing of plasticized PVC toys were derived for ATBC by using the data recently developed for DINP by the U.S. CPSC. Comparison of the EDIs derived for ATBC and ATBC's ADI indicate a low Relative Risk for long-term health effects in children using ATBC plasticized PVC toys.

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